FULL PAPER

Biliary dilatation in the presence of a periampullary duodenal diverticulum

J J LEE, MD, G BRAHM, MD, FRCPC, S G BRUNI, MD, S THIPPHAVONG, MD, FRCPC and B SREEHARSHA, MBBS, FRCPC

Department of Medical Imaging, University of Toronto, Toronto, ON, Canada

Address correspondence to: Dr Boraiah Sreeharsha
E-mail: boraiah.sreeharsha@uhn.ca

Jonghun John Lee and Boraiah Sreeharsha contributed equally to this article.

Objective: Periampullary diverticulum (PAD) often presents as an incidental CT finding. Its significance and its effect on biliary dilation are unclear. The aim of our study was to determine if the presence of a PAD is associated with abnormal dilation of the common bile duct (CBD).

Methods: Patients with PAD were retrospectively identified from the radiology database from November 2011 to November 2012 and those with known pancreaticobiliary pathology were excluded, except patients with cholelithiasis and prior cholecystectomy. A total of 150 patients with PAD were selected as well as a control group of 150 patients with no PAD. Data with respect to demographics, PAD size and location, ductal diameter, previous cholecystectomy and liver function tests were collected. To compare the groups, the Student’s t-test and χ² analysis were used where appropriate.

Results: The male:female ratio was 1:1.2 with a median average of 71 years in the PAD group. There was no statistical difference in the CBD measurement (at the pre-ampulla and pancreatic head, and distal to confluence) between the PAD and control groups (4.8, 6.9 and 6.8 mm for the PAD group; 4.7, 6.8 and 6.4 mm for the control group; p = 0.5, 0.7 and 0.3). Also, no difference was observed in the right and left intrahepatic biliary ducts (2.7, 2.7 mm for the PAD group; 2.5, 2.6 mm for the control group; p = 0.2, 0.6). There was a significantly higher incidence of cholecystectomy history (23% vs 8.7%, p < 0.01) and cholelithiasis (22% vs 11%, p < 0.01) in the PAD group, and no difference in the liver function tests. Subgroup analysis of small vs large PAD (<20 mm, ≥20 mm) did not show a difference in the CBD and intrahepatic biliary duct measurements. When comparing cholecystectomy vs non-cholecystectomy groups, CBD measurements were significantly higher in the cholecystectomy group.

Conclusion: Our study confirms that PAD on its own does not lead to abnormal CBD dilatation. However, increased incidence of cholelithiasis and cholecystectomy was noted in the presence of PAD.

Advances in knowledge: PAD on its own does not cause CBD dilatation.

INTRODUCTION

Periampullary diverticulum (PAD) is the second most common site of intestinal diverticulum formation after the colon, and it is usually an acquired lesion. PAD consists of pouches of mucosa, submucosa and muscularis mucosa that extend through the intestinal serosa, often within a radius of 3 cm from the ampulla of Vater. The incidence of PAD has been reported to be between 10% and 20% in the literature, depending on the type of study.1–3

The vast majority of patients with PAD are asymptomatic and are found incidentally. Previous studies have concluded that a diameter of either 1.5 or 2.0 cm should be used to classify small and large PAD,4,5 PAD originates at weak areas in the duodenal wall, which include perivascular connective tissue sheath pathways and the entrances of the common bile duct (CBD) and pancreatic duct.7 It has been previously shown that increasing age leads to increase in prevalence of PAD.7

Although a large majority of PAD are asymptomatic, association with various pancreaticobiliary complications is established in the current literature, including increased incidence of choledocolithiasis and pancreatitis.5,6 This is generally thought to be a consequence of both mechanical compression of the distal CBD as well as dysfunction of the sphincter of Oddi.7 Thus, radiologists are more permissive of dilated CBD in the presence of PAD when reporting. However, this dogma remains controversial owing to the confounding effects of age on the incidence of both PAD and bile stone pathogenesis, which is subsequently associated with higher rates of biliary obstruction, pancreatitis and therapeutic cholecystectomy.
To our knowledge, no study exists to date attempting to evaluate the effect of PAD on CBD diameter matched for age. In our current study, we investigate the effect of PAD on biliary duct calibre at multiple sites along the intrahepatic and extrahepatic biliary tract, as well as any relation to various clinical and biochemical markers of hepatobiliary dysfunction.

METHODS AND MATERIALS
This study was approved by the research ethics board at the University Health Network/Mount Sinai Hospital, Toronto, Canada. PAD was defined as any duodenal diverticulum within 1 cm from the ampulla of Vater. Patients with PAD were retrospectively identified from the radiology information system database from November 2011 to November 2012. The keywords “duodenal diverticulum” were used to identify patients who may have duodenal diverticulum from the radiology reports. Subsequently, CT images were reviewed to select only those with PAD as defined above. A total of 150 consecutive patients with PAD during this time period were included in the study. A control group of 150 patients with no PAD was selected from 1 November 2012 onwards—50 consecutive patients were selected from 3 hospital sites at the University Health Network (Toronto General Hospital, Toronto Western Hospital and Princess Margaret Hospital in Toronto, ON) for a total of 150 patients. The number of control groups was based on power calculations using average bile duct size and standard deviation of approximately 5 ± 2 mm based on findings of multiple prior studies examining average CBD size as assessed on CT to detect an average difference in bile duct diameter of 1 mm. To achieve a p < 0.05 and desired power of 0.90, average sample size required was 85 individuals. This value was approximately doubled to establish study and control group sizes.

Patients from both the PAD study group and control groups were excluded if there was a known history of hepatobiliary or pancreatic neoplasia, primary sclerosing cholangitis, recurrent pyogenic cholangitis, biliary stricture or complicated acute or chronic pancreatitis, as well as any relation to various clinical and biochemical markers of hepatobiliary dysfunction.

Data including age, gender, PAD size, PAD distance from CBD, PAD location, ductal diameter (proximal to the ampulla and pancreatic head, and distal to confluence), intrahepatic biliary duct diameter, history of cholecystectomy, the presence of gallstones and liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin] were recorded. The specific locations of the ductal diameter measurements are illustrated in Figure 1.

Descriptive statistics were reported as means and standard deviations for continuous variables and as a number and percentage for discrete variables. χ2 test or Fisher exact test, where appropriate, was conducted to compare discrete variables between groups. Student’s t-test was conducted for continuous variables, such as CBD diameter. Statistical analysis was carried out using SPSS® software v. 20 (SPSS Inc., Chicago, IL) to compare PAD and the effect on CBD. Statistical significance was defined as p < 0.05 (Figures 2 and 3).

RESULTS
Out of 150 patients with PAD, 68 (45%) were males and 82 (55%) were females, and the average age was 71 years (range 32–93 years). The average ductal diameter proximal to the ampulla, the pancreatic...
head and distal to confluence was 4.8, 6.9 and 6.8 mm, respectively. The average diameter of the right and left intrahepatic biliary ducts was both at 2.7 mm, and the average PAD size was 2.0 cm (range 0.5–6.7 cm). Approximately, 67% of PADs were located proximal to the ampulla of Vater and 33% located distally. 34 patients (23%) had a history of cholecystectomy and 22% had gallstones present on imaging. AST, ALT, ALP and total bilirubin were all within normal limits (Table 1).

The control group consisted of 74 males (49%) and 76 females (51%) and the average age was 69 years (range 34–93 years). The average ductal diameter proximal to the ampulla, the pancreatic head and distal to confluence was 4.7, 6.8 and 6.4 mm, respectively (p = 0.5, 0.7 and 0.3). The average intrahepatic biliary duct diameter was 2.5 mm for the right and 2.6 mm for the left. Cholecystectomy history was present in 13 cases (9%), and 16 patients had gallstones visible on imaging (11%). The liver function tests (AST, ALT, ALP and total bilirubin) were all within normal limits.

Owing to the control group being matched for age, there was no statistical difference with respect to age between the PAD and control groups (p = 0.2). Similarly, no difference in gender was observed (p = 0.5). The bile duct at the three different locations (proximal to the ampulla, pancreatic head and distal to confluence) demonstrated no significant difference between the two groups (p = 0.5, 0.7 and 0.3, respectively). In addition, the right and left intrahepatic ducts were not statistically different between the PAD and control groups (p = 0.2 and 0.6, respectively). More patients in the PAD group had a history of cholecystectomy than the control group (p < 0.01). In addition, more patients had gallstones on imaging in the PAD group (p < 0.01). The liver function tests (AST, ALT, ALP and total bilirubin) were similar between both the groups (p = 0.4 0.5, 0.06 and 0.8, respectively, Table 1).

A subgroup analysis was performed in the PAD group with PAD ≤ 20 mm and PAD > 20 mm. Patients in the large PAD group were older than patients in the small PAD group (76 years vs 68 years, p < 0.01). In addition, there was no difference in the ductal diameter at the three locations such as the proximal ampulla, the pancreatic head and distal to confluence (p = 0.9, 0.2 and 0.5, respectively). Similarly, there was no difference in the right and left intrahepatic biliary ducts (p = 0.5 and 0.9). No differences were observed with respect to prevalence of cholecystectomy (p = 0.6) nor gallstones (p = 0.5). Total bilirubin was significantly higher in the large PAD group at 12.3 µmolL⁻¹ than 9.0 µmolL⁻¹ in the small PAD group (p = 0.04). However, both levels were within normal limits. There was no difference in AST, ALT and ALP levels (p = 0.7, 0.2 and 0.1, respectively) (Table 2).

Out of the 300 patients involved in the study, they were also subdivided into cholecystectomy and non-cholecystectomy groups. In
the PAD group, 34 patients (23%) had a history of cholecystectomy (Table 3). There were more males in the cholecystectomy group than in the non-cholecystectomy group, and there was no difference with respect to age. The cholecystectomy group had significantly higher CBD diameter at the proximal ampulla, the pancreatic head and distal to confluence (p, 0.01) as well as the left and right intrahepatic biliary ducts (p, 0.01). The CBD diameter at the proximal ampulla, the pancreatic head and distal to confluence was 4.4, 6.4 and 6.2 mm, respectively, in the non-cholecystectomy group and 7.3, 9.4 and 10.1 mm for the cholecystectomy group. The right and left intrahepatic biliary ducts were 2.4 and 2.5 mm, respectively, for the non-cholecystectomy group and the cholecystectomy group had 4.1 and 4.2 mm. In addition, AST and ALT were higher in the cholecystectomy group (p, 0.01) and were higher than normal limits. Similar to the PAD group, no difference was observed between ALP and total bilirubin levels between the cholecystectomy and non-cholecystectomy groups.

**DISCUSSION**

By contrast to the commonly held conception that CBD diameter increases in the presence of PAD, our study, which to date is the only radiological study on this topic, demonstrates that the above-mentioned conception is not true. Our study shows that the biliary diameter in the absence of cholecystectomy is not affected or to be precise is not increased in the presence of PAD. Similar to some previous studies, our study is suggestive of a higher incidence of both cholelithiasis and cholecystectomy in the PAD group. However, there was no statistical difference with respect to the liver function tests (AST, ALT, ALP, total bilirubin).

In the control group, there were 13 patients (9%) with a history of cholecystectomy (Table 4). There was no difference with respect to gender and age. Similar to the PAD group, the cholecystectomy group had significantly higher CBD diameter at the proximal ampulla, the pancreatic head and distal to confluence (p, 0.01) as well as the left and right intrahepatic biliary ducts (p, 0.01). The CBD diameter at the proximal ampulla, the pancreatic head and distal to confluence was 4.4, 6.5 and 6.1 mm, respectively, in the non-cholecystectomy group and 7.3, 9.4 and 10.1 mm for the cholecystectomy group. The right and left intrahepatic biliary ducts were 2.4 and 2.5 mm, respectively, for the non-cholecystectomy group and the cholecystectomy group had 4.1 and 4.2 mm. In addition, AST and ALT were higher in the cholecystectomy group (p, 0.01) and were higher than normal limits. Similar to the PAD group, no difference was observed between ALP and total bilirubin levels between the cholecystectomy and non-cholecystectomy groups.

There are two leading theories that explain the pancreatobiliary disease associated with PAD. First, the presence of PAD may cause a mass effect and could cause mechanical obstruction of the sphincter of Oddi. Thus, there would be slowed biliary
excretion from PAD mass effect, leading to CBD dilatation as well as increased cholelithiasis. Alternatively, the other theory involves bacterial overgrowth in the diverticulum, which may lead to ascending infection to the biliary duct system. Skar et al.\textsuperscript{13} have demonstrated that higher levels of \( \beta \)-glucuronidase are found in patients with PAD than in control groups. The increased level of \( \beta \)-glucuronidase allows for the formation of free bilirubin, which can subsequently bind to calcium and form bilirubin stones. This is a more plausible explanation of the pathophysiology behind PAD as it explains both increased levels of cholelithiasis without significant change in the CBD diameter.

Chen et al.\textsuperscript{12} and Lotveit et al.\textsuperscript{14} suggested that there may be an increase in the CBD in the presence of PAD. However, the CBD measurements were not the focus of the study and no other studies investigating this relationship have been conclusive. Kennedy and Thompson\textsuperscript{15} compared 25 patients with and without PAD and reported an increasing trend of mean CBD diameter in patients with PAD, but not statistically significant. Lotveit et al.\textsuperscript{12} compared a total of eight patients with PAD with eight controls, which revealed a possible increase in CBD in the PAD group, but statistical analysis was not performed. In addition, Chen et al.\textsuperscript{12} reported that the incidence of PAD was higher in patients with CBD dilatation (27/110 patients) than those who did not have CBD dilatation (5/54 patients), with reported statistical significance \( p < 0.05 \). However, only a small number of patients in this series (27 patients) had PAD and age was not adjusted in the control group. The most recent study by Kim et al.\textsuperscript{16} has suggested that there is an association between large PAD and dilated CBD based on a total of 74 cases. Similar to the previous studies, age was not matched in the control group. It is well established that incidence of both diverticula and bile duct diameter rises with increasing age and thus the results of prior studies, which have failed to control for this confounding variable are ambiguous. Alternatively, our study is the first and the largest \( (n = 150 \) for the study group and control) to demonstrate that no significant difference in ductal diameter at multiple sites with an age- and gender-matched control groups exists.

### Table 2. Demographics, clinical characteristics and bile duct measurements according to periampullary diverticulum (PAD) size (<20 mm and ≥20 mm)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAD &lt;20 mm ((n = 87))</th>
<th>PAD ≥20 mm ((n = 63))</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Male</td>
<td>40 (46.0)</td>
<td>28 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47 (54.0)</td>
<td>35 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Age (years; median, range)</td>
<td>67.9 ± 11.8</td>
<td>75.3 ± 9.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>PAD size (mm)</td>
<td>12.5 ± 4.6</td>
<td>31.0 ± 9.9</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>PAD distance from CBD (cm)</td>
<td>2.1 ± 1.9</td>
<td>2.5 ± 2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>PAD location (pre vs post)</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Pre</td>
<td>58 (67.0)</td>
<td>35 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>28 (32.3)</td>
<td>28 (44.4)</td>
<td></td>
</tr>
<tr>
<td>CBD diameter (proximal ampulla, mm)</td>
<td>4.9 ± 2.5</td>
<td>4.8 ± 2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>CBD diameter (pancreatic head, mm)</td>
<td>6.7 ± 2.7</td>
<td>7.2 ± 3.0</td>
<td>0.2</td>
</tr>
<tr>
<td>CBD diameter (distal to confluence, mm)</td>
<td>6.6 ± 3.0</td>
<td>7.0 ± 2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Right intrahepatic biliary duct (mm)</td>
<td>2.7 ± 2.0</td>
<td>2.9 ± 2.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Left intrahepatic biliary duct (mm)</td>
<td>2.7 ± 1.9</td>
<td>2.7 ± 1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Cholecystectomy history</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (24.1)</td>
<td>13 (20.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>66 (75.9)</td>
<td>50 (79.4)</td>
<td></td>
</tr>
<tr>
<td>Gallstones on imaging</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (19.5)</td>
<td>16 (25.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67 (77.0)</td>
<td>47 (74.6)</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>27.0 ± 33.7</td>
<td>25.1 ± 20.9</td>
<td>0.7</td>
</tr>
<tr>
<td>ALT</td>
<td>28.1 ± 46.9</td>
<td>20.1 ± 15.0</td>
<td>0.2</td>
</tr>
<tr>
<td>ALP</td>
<td>88.5 ± 54.4</td>
<td>104.0 ± 66.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>9.0 ± 4.0</td>
<td>12.3 ± 12.3</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct.
As with the relationship of PAD to CBD, the association of PAD with increased incidence of cholelithiasis is similarly controversial. Hagege et al. indicate that the prevalence of PAD was increased in choledocholithiasis but not cholelithiasis. Other studies have also supported this finding. However, there have been a few comparative studies describing a possible relationship between PAD and cholelithiasis under strict matching for sex and age. Egawa et al. demonstrated that large PAD may play a role in the formation of cholelithiasis in a total of 83 patients with PAD. We report that cholelithiasis occurrence is significantly higher in the PAD group than in the control group. In addition, more patients in the PAD group may have had higher incidence of cholelithiasis in the past.

The obvious limitations of the study are the single-centre analysis and retrospective nature of the analysis. In radiology reports, not all PADs are mentioned, thus, patients with PAD may have been missed during recruitment. Also, the assessment of stones was based solely on CT findings and from ultrasound reports and not all patients had

| Table 3. Demographics, clinical characteristics and bile duct measurements according to cholecystectomy and non-cholecystectomy groups in the periampullary diverticulum group |
|-----------------------------------------------|-----------------|----------------|-----------------|
| **Parameter**                      | **Cholecystectomy (n = 34)** | **No cholecystectomy (n = 116)** | **p-value** |
| Gender                               | Male 22 (64.7)    | 46 (39.7)    | 0.01*           |
|                                      | Female 12 (35.3)  | 70 (60.3)    |                 |
| Age at diagnosis (years; median, range)| 71.0 ± 11.8      | 71.1 ± 11.6  | 0.94            |
| CBD diameter (proximal ampulla, mm)  | 6.3 ± 3.3        | 4.4 ± 2.1    | <0.01*          |
| CBD diameter (pancreatic head, mm)   | 8.7 ± 3.1        | 6.4 ± 2.5    | <0.01*          |
| CBD diameter (distal to confluence, mm)| 8.9 ± 3.5    | 6.2 ± 2.4    | <0.01*          |
| Right intrahepatic biliary duct (mm) | 4.2 ± 2.4        | 2.3 ± 1.6    | <0.01*          |
| Left intrahepatic biliary duct (mm)  | 4.0 ± 2.1        | 2.3 ± 1.6    | <0.01*          |
| AST                                   | 33.9 ± 49.3      | 24.0 ± 19.1  | 0.08            |
| ALT                                   | 37.1 ± 71.7      | 21.1 ± 16.2  | 0.03*           |
| ALP                                   | 106.5 ± 84.4     | 91.6 ± 51.1  | 0.2             |
| Total bilirubin                       | 9.3 ± 7.3        | 10.8 ± 9.2   | 0.4             |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct.

As with the relationship of PAD to CBD, the association of PAD with increased incidence of cholelithiasis is similarly controversial. Hagege et al. indicate that the prevalence of PAD was increased in choledocholithiasis but not cholelithiasis. Other studies have also supported this finding. However, there have been a few comparative studies describing a possible relationship between PAD and cholelithiasis under strict matching for sex and age. Egawa et al. demonstrated that large PAD may play a role in the formation of cholelithiasis in a total of 83 patients with PAD. We report that cholelithiasis occurrence is significantly higher in the PAD group than in the control group. In addition, more patients in the PAD group may have had higher incidence of cholelithiasis in the past.

The obvious limitations of the study are the single-centre analysis and retrospective nature of the analysis. In radiology reports, not all PADs are mentioned, thus, patients with PAD may have been missed during recruitment. Also, the assessment of stones was based solely on CT findings and from ultrasound reports and not all patients had

| Table 4. Demographics, clinical characteristics and bile duct measurements according to cholecystectomy and non-cholecystectomy groups in the control group |
|-----------------------------------------------|-----------------|----------------|-----------------|
| **Parameter**                      | **Cholecystectomy (n = 13)** | **No cholecystectomy (n = 137)** | **p-value** |
| Gender                               | Male 4 (30.8)    | 70 (51.1)    | 0.2             |
|                                      | Female 9 (69.2)  | 67 (48.9)    |                 |
| Age at diagnosis (years; median, range)| 67.3 ± 11.1      | 69.4 ± 13.3  | 0.6             |
| CBD diameter (proximal ampulla, mm)  | 7.3 ± 2.6        | 4.4 ± 1.7    | <0.01*          |
| CBD diameter (pancreatic head, mm)   | 9.4 ± 2.5        | 6.5 ± 2.0    | <0.01*          |
| CBD diameter (distal to confluence, mm)| 10.1 ± 3.3  | 6.1 ± 2.2    | <0.01*          |
| Right intrahepatic biliary duct (mm) | 4.1 ± 1.3        | 2.4 ± 1.3    | <0.01*          |
| Left intrahepatic biliary duct (mm)  | 4.2 ± 1.3        | 2.5 ± 1.2    | <0.01*          |
| AST                                   | 154.3 ± 406.5    | 24.7 ± 15.0  | <0.01*          |
| ALT                                   | 167.6 ± 456.6    | 21.6 ± 16.6  | <0.01*          |
| ALP                                   | 97.9 ± 53.3      | 81.7 ± 36.9  | 0.2             |
| Total bilirubin                       | 10.0 ± 4.9       | 10.2 ± 5.6   | 0.9             |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, common bile duct.
ultrasound. Ultrasound reports were used in conjunction with the findings on CT to assess for the presence of cholelithiasis. While the cohort size might be considered small in certain contexts, this actually represents the first and the largest reported to date comparing CBD size according to PAD matched for age and gender.

Overall, this study strongly demonstrates that PAD on its own does not lead to abnormal biliary dilatation, and as such one cannot simply dismiss or otherwise ascribe duct dilatation to the presence of PAD. In addition, we once again provide further suggestion that PAD is associated with increased incidence of cholelithiasis.

FUNDING
This article was funded by Department of Medical Imaging, University of Toronto, Toronto, ON, Canada.

REFERENCES


